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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/793,653	02/27/97	DE SAUVAGE	F	PT985P2

HM21/0527

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EXAMINER	
DRAPER, G	
ART UNIT	**PAPER NUMBER**
1646	3

DATE MAILED: 05/27/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-27 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-27 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

Part III: Detailed Office Action

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Group 1640, Technology Center 1600.

2. Restriction Requirement:

This application was filed under 35 USC 37, therefore, all of the claims of record will be examined.

3. Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. A new title that is more specific to the invention is required such as "Ob-Ig Chimers, Nucleic Acids encoding such, PEG-Conjugates and Compositions"

Claims 25 appears to be improperly dependent on claim 20, which is a host cell claim. It would appear that this claim should depend from claim 24.

Claim 21 appears to be improperly dependent on claim 16, which is the chimer. It would appear that this claim should depend from claim 20

4. Double Patenting Rejections:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal

disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-23, 26, 28-41 of copending Application No.08/667184 . Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to the claims of the co-pending application, because they are directed to the use of any Ob protein, wherein the characteristics have not been set forth, and they refer to the fusion of the Ob protein to the c-terminal of the Ig. The instant claims overlap in scope with those of the copending application. Therefore, it would have been obvious to use the specific Ob protein and fuse it to any part of the Ig from the copending application in order to obtain the broad claims to the use of any Ob protein that is conjugated to the Ig at the known and conventional sites.

ABN

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Objections and Rejections under 35 U.S.C. §112:

Claims 7-9 are objected to as being substantial duplicates of claim 1 despite the slight difference in the wording, and irrespective to the statements of intended use or the preamble recitation. Each claims is directed to the Ob derivatives (see MPEP 706.03(k).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As written the claim is confusing and indefinite and incomplete for failing to state what the process is for, such as "a process of preparing/making" etc. Since this claim appears to be directed to a method of preparing the chimer, it is incomplete for failing to recite a recovery

step, which ensures that the chimer is prepared. Thus, the recitation of a recovery or isolation step would obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nature form of the Ob protein and certain limited derivatives fused to Ig or PEG, does not reasonably provide enablement for: a) any long half-life derivative in which the make-up of the protein and/or fusion partner is not set forth, nor is there enablement for any Ob protein having a sequence that binds to the Ob receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-3, 7-12 and 27 are generic to a long half-life derivative of the Ob protein, but fail to recite to make-up of this product. From the specification, all that applicants have enabled is the fusion of conjugation of specific Ob protein to Ig or to PEG in order to improve on their half-life. However, the claims are broader than this, and as written, the claims do not even require the presence of a fusion or conjugated partner to effect this improvement in the half-life. In the absence of the claims to recite a partner that will achieve such, the claims are not enabled, because there is nothing in the specification to teach or suggest that the Ob per se or a modified/mutated form of the Ob protein will have improved half-life. Furthermore, the enablement for the fusion/conjugation of the Ig or PEG to the Ob protein is not sufficient such that they could reasonably predict that other agents or protein can be fused/conjugated to the Ob protein in order to impart this property. Therefore these claims are not enabled for their full scope.

Claims 1-27 are also not enabled for the full scope of the Ob protein that can be

derivitized in order to have a product with the improved half-life. While applicants have shown that the mature form of the Ob protein can be fused to the Ig or PEG and still maintain the activity of the protein, these results are not sufficient to be reasonably predictive of the use of any Ob protein that will bind to the cognate receptor. The Ob protein is approximately 145 amino acids long, and at the time of filing it was shown to posses different activities. There are not structure/function studies of record to teach or predict where the receptor binding regions are, or where other biologically active residues residue. Therefore, in the absence of the such, it would constitute undue experimentation for the skilled artisan to determine such without sufficient examples or guidance in order to produce the desired chimers or conjugates that will possess the desired receptor-binding activity and biological activity. Since the claims encompass substitutions, insertions, and deletions mutants/derivatives, in the absence of evidence for where the critical regions are, and whether these regions can tolerate the various changes, it would constitute undue experimentation for the skilled artisan to go about picking and choosing regions that can tolerate modifications or deletions, and for the preparation and testing of each to ensure that they possess the desired activity. Since the claims fail to recite any physical or functional characterizing features for the protein, and merely recite an acronym, this allows the claims to encompass any protein that is known as Ob, yet the specification is not enabled for such. Therefore, the claims should be amended to recited a reasonable amount of characteristic and of such scope that is enabled by the specification.

6. ***Rejections Over Prior Art:***

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

NOTE: Claims 1-3, 7-9, 10-12 and 27 are generic to a long half-life derivative of the Ob protein and the use of such, wherein a conjugating or fusion agent is not recited in the claims, thus, these generic claims will be rejected with the art of the Ob-PEG conjugates, as well as the art of the Ob-Ig chimers/fusions.

Claims 1-3, 5-12 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Zhang et al, DiMarchi et al or Basinski et al in view of any one of Hakimi et al (`356), Greenwald et al (`924), Haratani (`546), Nishimura et al (`316), Davis et al (`337), Yamasaki et al (1988 or 1990) or Francis.

Each of the primary reference disclose mutant forms of the Ob polypeptide (see the claims in the various patents). Also taught is that these mutants can be formulated into the various known pharmaceutical formulations for the administration in various ways ,such as soluble and insoluble forms. These compositions can be used to treat weight disorders (see for example col 13-14 in 5580954, and similar teachings in the others primary references). Not specifically taught by the primary references is the formulation of the mutant Ob proteins as polymer (PEG) conjugates wherein such conjugation provides various enhanced benefits for therapeutic use. EACH of the secondary references provide a wide variety of teaching for conjugating various proteins to polymer conjugates for enhance bioavailibility and to enhance other properties of the protein when used therapeutically.

Although the claims recite statements of intended use, routes of administrations and amounts, and conditions for treatment, the preamble refers to composition, thus the claims are not directed to methods and such limitations have not been given weight because the composition per se would be the same irrespective of any statements of intended use. No one prior art

individually disclose each aspect of the invention, however, at the time of the invention it would have been prima facie obvious to use the teachings of the secondary references and conjugate polymers to the Ob mutants of the primary references because these secondary references teach the advantage of formulating polymers to different proteins in orders to achieve a number of advantages from such protein therapy. Furthermore, each of the primary references teach that the Ob mutants could be formulated in a number of ways conventionally known in the art for use to treat weight disorders, wherein such formulation, while not expressly teaching the conjugation to polymers, include insoluble forms that would be representative of the PEG conjugates. Therefore, the skilled artisan would have been motivated by the combined teachings of both the primary and secondary reference for conjugating the Ob mutant of the primary to the various polymers of the secondary reference, and would have reasonably expected that such conjugation would have provided an additional benefit form use therapeutically.

Claims 1-3, 7-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al, Basinski et al ('744 or '886), DiMarchi et al ('954 or '336), in view of Shin et al or Ashkenozi et al.

Each of the primary references disclose the mature form of the human and murine Ob protein, or mutant forms of the Ob protein (see the entire documents of each). Also taught is that these Ob protein can be used to modulate weight (see the results sections of each). Not taught by these primary references is the conjugation of the Ob protein to an Ig, or how it is to be conjugated; however, each of the secondary references teach the concept of fusing immunoglobulin or their single chains to various mature proteins or polypeptides for the use in therapy or for use diagnostically. Each of the secondary references appear to be generic in their teachings, and the methods for making the fusion or chimeric protein are disclosed, as well as the advantages for doing such (see the entire documents of each).

No one prior art individually disclose each aspect of the invention in its entirety, however, at the time of the invention it would have been prima facie obvious and the skilled artisan would have been motivated to fuse the Ob protein or Ob mutants of the primary

references to Ig in a manner as taught and for the advantages that are taught by the secondary references. This prima facie case of obvious is also supported by the teachings of the primary references for the potential benefits of using these protein. Furthermore, the skilled artisan would have also expected that the processes of the secondary references could have been used with the ob protein of the primary references, because the broad and generic teachings of the secondary references teach that such conjugates can be made with different protein, wherein in the advantages (improvements in the properties of the protein, as well as the immunoglobulin) associated with these conjugates is generally imparted to all such conjugates irrespective of the protein that is being used.

7. Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to **Garnette D. Draper, Art Unit 1646, whose telephone number is (703) 308-4232.** Examiner Draper can normally be reached Monday through Friday, 9:30 A.M. to 6:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

GARNETTE D. DRAPER
PRIMARY EXAMINER
GROUP 1800